REMARKS

This invention is directed to methods of treating renal fibrosis by the administration of quinazolinones. The specification and examples demonstrate the efficacy of halofuginone, a species of quinazolinone, for inhibition of the pathological progression of renal fibrosis.

Claim amendments:

The phrase "in need thereof" has been moved to a new place in claim 9 in order to overcome the Examiner's objection for lack of antecedent basis for the term "the subject in need thereof". The phrase "of a subject" has been inserted into claim 15 in order to overcome the Examiner's objection for lack of antecedent basis for the term "said subject".

Applicants have also deleted the clause, "wherein the step of administering the compound is performed before the subject exhibits a renal fibrotic condition" to clarify that the compound of the invention can be administered at any time during the progression of the disease state.

Reply to the Examiner's Rejections:

The Examiner has rejected claims 9-11 and 15-17 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,449,678 ("Pines"). According to the Examiner, because Pines would have suggested to the ordinary skilled worker that "the progression of renal fibrosis could be attenuated" by halofuginone treatment, because Pines teaches that halofuginone is "a specific α1 type I collagen synthesis inhibitor" which decreases fibrosis by

decreasing collagen type I synthesis. The Examiner further states that Pines provides the claim requirement, "preserving renal function following exposure to an inducer of renal fibrosis" because Pines teaches that "progressive fibro-proliferative diseases exhibit excessive production of connective tissues which results in destruction of normal tissue architecture and function." (Office Action, pages 2-4). Applicants respectfully disagree.

The present application relates to the attenuation of renal fibrosis with quinazolinone derivatives such as halofuginone as well as pharmaceutical compositions for administration of halofuginone to a patient. The specification discloses that halofuginone may act by inhibiting collagen type I synthesis, but other as yet undetermined mechanisms may also be involved, as indicated by the fact that other inhibitors of collagen synthesis have not proven effective in the attenuation of renal fibrosis.

The present application also distinguishes Pines, and in particular, addresses the difficulties in predicting the *in vivo* effects of Halofuginone based on results of *in vitro* experiments:

> Notably, the *in vitro* action of Halofuginone does not always predict its *in vivo* effects. For example, as demonstrated in U.S. Patent No. 5,449,678, halofuginone inhibits the synthesis of collagen type I in bone chondrocytes *in vitro*. However, chickens treated with halofuginone were not reported to have an increased rate of bone breakage, indicating that the effect is not seen *in vivo*.

Page 3, lines 4-8.

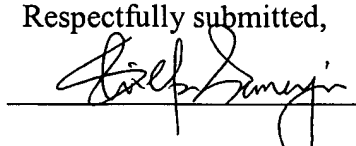
Pines reports the *in vivo* effects of halofuginone on skin fibroblasts and chondrocytes. Pines does not, however, demonstrate that halofuginone would be effective in an

in vitro (or *in vivo*) tissue culture assay with kidney or other similar types of cells. As stated in the present application, results obtained with *in vitro* experiments using fibroblasts are not necessarily predictive of the behavior of kidney cells after contact with halofuginone *in vivo*.

A reference cited to reject claims based on § 103(a) obviousness must not only suggest the treatment of renal fibrosis with Halofuginone, it must also provide a reasonable expectation of success that administration of Halofuginone to an individual suffering from the renal fibrosis would be successful in treating or preventing the disease. Pines is a general approach. That is insufficient. A general approach amounts only to an "obvious-to-try" situation -- a standard for obviousness that has been repeatedly rejected. *Gillette Co.* v. *S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed.Cir. 1990) ("An 'obvious-to-try situation' exists when a general disclosure may pique the scientist's interest ..."). Pines, based merely on its effects on avian skin fibroblasts and chondrocytes, does not provide a reasonable expectation of success that administration of halofuginone to a patient would effectively attenuate renal fibrosis. Therefore Pines cannot amount to a teaching that the use of Halofuginone can attenuate renal fibrosis *in vivo*, as disclosed and taught in the present application. Accordingly, the present invention is not obvious in view of Pines.

Applicants request that the Examiner consider the foregoing amendments and remarks and pass this application to issue. A telephonic interview with applicants' representative is kindly requested if it would help the Examiner in placing the claims in condition for allowance.

Respectfully submitted,



Jane T. Gunnison (Reg. No. 38,479)
Barbara A. Ruskin (Reg. No. 39,350)
Shilpi Banerjee (Reg. No. 53,965)
Attorneys for Applicants

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1105
Tel.: (212) 596-9000
Fax: (212) 596-9090